Docket No.: 026220.00073
(PATENT)

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

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| In re Patent Application of: | Attorney Docket No. 026220.00073 |
| Nicoletta ALMIRANTE et al. | Confirmation No.: 1937 |
| Application No.: 10/566,292 | Art Unit: 1626 |
| Filed: January 27, 2006 | Examiner: J. R. Kosack |

For: NITROOXY DERIVATIVES OF LOSARTAN, VALSARTA, CANDESARTAN, TELMISARTAN, EPROSARTAN AND OLMESARTAN AS ANGIOTENSIN-II RECEPTOR BLOCKERS FOR THE TREATMENT OF CARDIOVASCULAR DISEASES

## APPEAL BRIEF

**MS Appeal Brief - Patents**
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Date: June 22, 2010

Sir:

Submitted herewith is an Appeal Brief with concurrent payment of the official fees for the Appeal Brief. Please charge any fee deficiencies required with respect to this paper, or overpayment to our Deposit Account No. 01-2300, referencing docket number 026220-00073.

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## I. INTRODUCTION

This is an appeal from the Advisory Action dated March 10, 2010, and the Final Office Action dated November 23, 2009. Claims 1, 2, 5-15, and 18 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over McIntyre et al. (Pharmacol. Ther., 74(2): 181-184 (1997), hereinafter "McIntyre") in view of Del Soldato (PCT Application Publication No. WO 00/61537, hereinafter "Del Soldato I") and Del Soldato (PCT Application Publication No. WO 95/09831, hereinafter "Del Soldato II"). .

A Notice of Appeal was timely filed on April 23, 2010, with the appropriate fees. As such, the Appellants Brief on Appeal is being timely filed.

## II. REAL PARTY IN INTEREST

The real party in interest in the present application is the assignee, Nicox S.A., of Sophia Antipolis-Valbonne, France, as evidenced by the assignment recorded at the United States Patent and Trademark Office on December 1, 2006, at reel 018700, frame 0268.

## III. RELATED APPEALS AND INTERFERENCES

The appellants, appellants' legal representative, and assignees are not aware of any related appeals or interferences that will directly affect, or be directly affected by, or have a bearing on the Board's decision in the pending appeal.

## IV. STATUS OF CLAIMS

Claims 1-3 and 5-21 are pending. Claims 3, 16, 17, and 19-21 are withdrawn from consideration. Claims 1, 2, 5-15, and 18 are rejected. Claims 1, 2, 5-15, and 18 are being appealed. A copy of the claims under appeal can be found in Appendix A.

## V. STATUS OF AMENDMENTS

No amendments have been filed subsequent to the Final Office Action of November 23, 2009 and the Advisory Action of March 10, 2010, from which this appeal has been taken.

## VI. SUMMARY OF THE CLAIMED SUBJECT MATTER ON APPEAL

The subject matter of independent claims 1 and 15 and dependent claims 2, 5-14, and 18 is directed to nitroderivatives of Angiotensin II Receptor Blockers.

Specifically, independent claim 1 is directed to the compounds of formula (I), R-$(Y\text{-}ONO_2)_s$, wherein s = 1 or 2, R is an Angiotensin II Receptor Blocker of formula (II) or (III), and Y is a bivalent radical (pages 2-4 of the Specification). The definition of R can be found in the Specification, for example, at page 2, last paragraph through page 4, first paragraph. The definition of Y can be found in the Specification, for example, at page 4, second paragraph through page 7, fifth paragraph. Independent claim 1 is also directed to pharmaceutically acceptable salts and stereoisomers of the compounds of formula (I). Examples of the compounds encompassed by claim 1 can be found in the Specification, for example, at pages 10-37.

Independent claim 15 is directed to the compound of formula (2) disclosed in Example 2 of the Specification (page 10 and pages 52-57).

In response to the Restriction and Election of Species Requirement dated July 7, 2008, Appellants elected Group I drawn to the compounds of formula (I) where R is formula (II) and R1 is formula (IIa). In response to the Election of Species Requirement, Appellants provisionally elected compound (2) of Example (2) of the present invention. Thus, at the present time, compound (2) disclosed, for example, on page 10 and page 52 of the Specification is under consideration.

## VII. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

(1) Whether claims 1, 2, 5-15 and 18 are unpatentable under 35 U.S.C. § 103(a) over McIntyre et al. (Pharmacol. Ther., 74(2): 181-184 (1997), hereinafter "McIntyre") in view of Del Soldato (PCT Application Publication No. WO 00/61537, hereinafter "Del Soldato I") and Del Soldato (PCT Application Publication No. WO 95/09831, hereinafter "Del Soldato II").

## VIII. ARGUMENT

### A. Legal Overview

When rejecting claims under 35 U.S.C. §103, an Examiner bears an initial burden of presenting a *prima facie* case of obviousness. If an Examiner fails to establish a *prima facie* case, the rejection is improper and will be overturned. See *In re Rijckaert*, 9 F.3d 1531, 1532, 28 U.S.P.Q. 2d. 1955 (Fed. Cir. 1993). "If examination.... does not produce a *prima facie* case of unpatentability, then without more the applicant is entitled to the grant of the patent." *In re Oetiker*, 977 F.2d 1443, 1445 – 1446, 24 U.S.P.Q. 2d. 1443, 1444 (Fed. Cir. 1992).

Several basic factual inquiries must be made to determine obviousness or non-obviousness of patent application claims under 35 U.S.C. §103. These factual inquiries are set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 17 (1966):

> Under § 103, the scope and content of the prior art are to be determined; differences between the prior art and the claims at issue are to be ascertained; the level of ordinary skill in the pertinent art resolved. Against this backdrop, the obviousness or non-obviousness of the subject matter is determined.

Appellants respectfully submit that the specific factual inquiries set forth in *Graham* have not been considered or properly applied by the Examiner formulating the rejection of the pending claims. Particularly the scope and content if the prior art and differences between the prior art and the claims were not properly determined. As stated by the Federal Circuit in *In re Ochiai*, 37 U.S.P.Q. 2d 1127, 1131 (Fed. Cir. 1995):

> [t]he test of obviousness *vel non* is statutory. It requires that one compare the claim's subject matter as a whole with a prior art to which the subject matter pertains. 35 U.S.C. § 103.
>
> The inquiry is highly fact-specific by design.... When the references cited by the Examiner fail to establish a *prima facie* case of obviousness, the rejection is improper and will be overturned. *In re Fine*, 837 F.2d 1071, 1074, 5 U.S.P.Q. 2d 1596, 1598 (Fed. Cir. 1988). (Emphasis added.)

A *prima facie* case of obviousness is established only if the teachings of the prior art as a whole would have suggested the claimed subject matter to a person of ordinary skill in the art. The proper analysis is whether the claimed invention would have been obvious to one of ordinary skill in the art after consideration of all the facts. See *Examination Guidelines for Determining Obviousness Under 35 U.S.C. 103 in View of the Supreme Court Decision in KSR International Co. v. Teleflex Inc.*, Federal Register/Vol. 72, No. 195/Wednesday, October 10, 2007/Notices, p. 57528. Further, in *KSR*, the Supreme Court held that "[t]he obviousness analysis cannot be confined by a formalistic conceptions of the words teaching, suggestion, and motivation, or by

overemphasis on the importance of published articles and the explicit content of issued patents."

Appellants respectfully submit that the Examiner has not made a proper *prima facie* rejection under 35 U.S.C. §103(a), because the combination of prior art reference fails to teach or suggest the presently claimed invention.

B. Rejection of claims 1, 2, 5-15 and 18 under 35 U.S.C. §103

As noted above, compound (2) ("the elected species") is currently under examination. Compound (2) is a derivative of losartan, whereby an $ONO_2$ group is attached to the base molecule via a spacer group, which the Examiner refers to as a nitrooxy tether. With respect to the elected species, the Examiner concedes that McIntyre does not teach or suggest attaching a nitroxy tether to losartan. However, the Examiner refers to pages 6-13 of Del Soldato I and alleges that Del Soldato I specifically mentions losartan as a drug capable to be modified by attaching a nitrooxy tether (Office Action of November 23, 2009, page 2, last paragraph, and page 4, paragraph 5). Appellants respectfully disagree with the Examiner's determination of the scope and content of the prior art.

Del Soldato I discloses losartan in two contexts. In the first context, Del Soldato I discloses losartan solely to support the assertion that the conventionally used drugs show lower activity and/or higher toxicity in various pathological conditions associated with oxidative stress. Here, Del Soldato I discloses losartan amongst several different classes drugs that show lower activity and/or higher toxicity in oxidative stress associated with various pathological conditions (pages 1-7 of Del Soldato I) and does not disclose or teach that losartan can be nitrooxy-modified.

In the second context, Del Soldato I discloses losartan along with several hundreds of drugs that may be used as a precursor drug for preparing the compounds of Del Soldato I. In this case, page 41 of Del Soldato I discloses losartan along with a vast number of other drugs listed on page 38 through page 49. However, as discussed below, Del Soldato I does not disclose or teach whether the drugs listed on pages 38-49

including losartan can satisfy at least one of the three tests specifically required by Del Soldato I for selecting precursor drugs.

Del Soldato I discloses that for a drug to be selected as a precursor drug, it must meet at least one of the following 3 tests: NEM test (test 1), CIP test (test 2), and L-NAME test (test 3) (pages 13-16 and pages 27-32). On pages 34-35 and in Examples F1-F3, Del Soldato I demonstrates that certain drugs such as indomethacin, paracetamol, mesalmine satisfy at least one of the three tests and therefore can be used as precursor drugs while some other drugs such as omeprazol or misoprostol do not satisfy any one of the three tests and therefore cannot be used to prepare the compounds of Del Soldato I. However, both omeprazol and misoprostol are included in the laundry list of drugs disclosed by Del Soldato I on pages 38-49 as potential precursor drugs (page 43, anti-ulcer drugs). In view of this contradictory disclosure of Del Soldato I, the skilled artisan would have to test each and every drug listed on pages 38-49 to decide whether it would qualify as a precursor drug. Thus, in contrast to the Examiner's assertion, the mere disclosure of losartan as one of several hundreds of potential precursor drugs does not specifically teach or suggest that losartan can be modified by attaching a nitrooxy tether.

Furthermore, Del Soldato I does not provide any teaching or suggestion to select losartan from the number of drugs disclosed in Del Soldato I. Specifically, the drugs that meet at least one of the three tests required by Del Soldato I are disclosed on pages 34-35 and in Examples 1-26 and F1-F3 of Del Soldato I. However, there is no structural similarity between the above precursor drugs of Del Soldato I and losartan. This structural dissimilarity between the precursor drugs specifically disclosed in Del Soldato I and losartan would not have motivated the skilled artisan to select losartan for nitrooxy modification from the vast number of drugs disclosed in Del Soldato I.

Given the contradictory nature of the Del Soldato I disclosure, and the fact that the drugs specifically disclosed in Del Soldato I are structurally and chemically completely different from losartan, the skilled artisan would not have been motivated to select losartan for attaching a nitrooxy tether. Moreover, neither McIntyre nor Del

Soldato II alone or in combination overcomes the above discussed deficiencies of Del Soldato I.

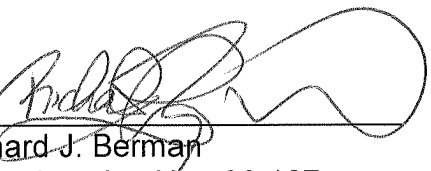
For at least, the above reasons, Appellants submit that independent claims 1 and 15 are not obvious over the combination of McIntyre, Del Soldato I and Del Soldato II. Claims 2, 5-14, and 18 because of their dependence from claim 1 are also not obvious over the combination of the cited references. Accordingly, Appellants respectfully request this Board to reverse the Examiner with respect to the rejection of claims 1, 2, 5-15 and 18 under 35 U.S.C. § 103(a) over McIntyre in view of Del Soldato I and Del Soldato II.

## IX. CONCLUSION

For all of the above-noted reasons, it is strongly contended that clear differences exist between the present claimed invention and the prior art asserted by the Examiner. It is further contended that these differences are such that the present invention would not have been obvious to a person having ordinary skill in the art at the time the invention was made. Accordingly, Appellants respectfully submit that claims 1, 2, 5-15 and 18 are not obvious under 35. U.S.C. § 103(a) and respectfully request the Honorable Board of Patent Appeals and Interferences to reverse the rejection.

Applicant believes no fee is due with this response. However, if a fee is due, please charge our Deposit Account No. 01-2300, referencing Attorney Docket. No. 026220.00073.

Respectfully submitted,



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APPENDIX A: COPY OF THE CLAIMS INVOLVED IN THE APPEAL

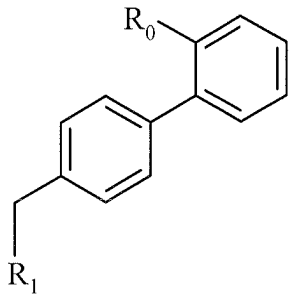
Claim 1. (Previously Presented) A compound of general formula (I) or a pharmaceutically acceptable salt or stereoisomer thereof:

$$R\text{-}(Y\text{-}ONO_2)_s \quad (I)$$

wherein:

s is an integer equal to 1 or 2;

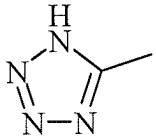
R is selected from the following Angiotensin II Receptor Blocker residues of formula (II) or (III):



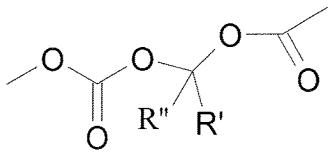
(II)

wherein:

$R_0$ is

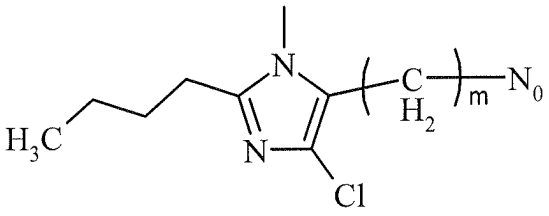


or $-N_0$ which is a group capable to bind to Y, having one of the following meaning: -COO-, -O-, -CONH-, –OCO-, -OCOO- or

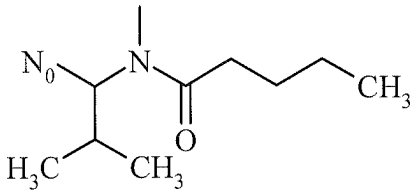


wherein R' and R'' are the same or different, and are H or straight or branched $C_1$-$C_4$ alkyl;

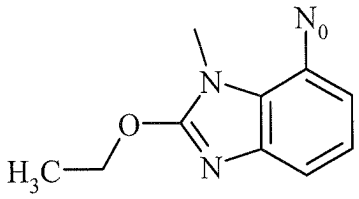
$R_1$ is selected from the group consisting of:



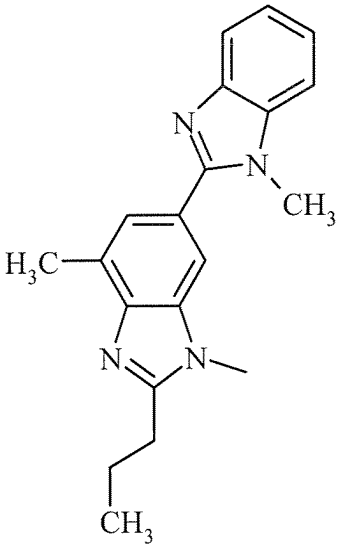
(IIa)



(IIb)

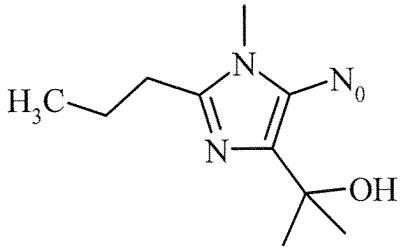


(IIc)



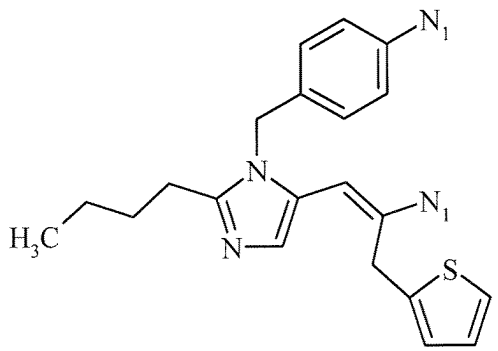
(IId)

or



(IIe)

wherein m is an integer equal to 0 or 1 and $N_0$ is as above defined;



(III)

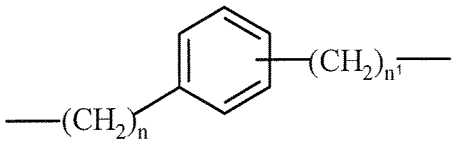
wherein $N_1$ has the same meaning as $N_0$ or is equal to -COOH; with the proviso that at least one of the groups $N_1$ is equal to -COO- or –CONH-, i.e. it is a group capable to bind to Y;

Y is a bivalent radical having the following meaning:

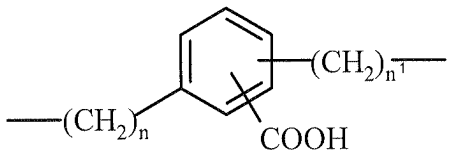
a)

- straight or branched $C_1$-$C_{20}$ alkylene, being optionally substituted with one or more of the substituents selected from the group consisting of: halogen atoms, hydroxy, $–ONO_2$ or $T_0$, wherein $T_0$ is $–OC(O)(C_1$-$C_{10}$ alkyl)-$ONO_2$ or $–O(C_1$-$C_{10}$ alkyl)-$ONO_2$;
- cycloalkylene with 5 to 7 carbon atoms into cycloalkylene ring, the ring being optionally substituted with side chains T, wherein T is straight or branched alkyl with from 1 to 10 carbon atoms;

b)

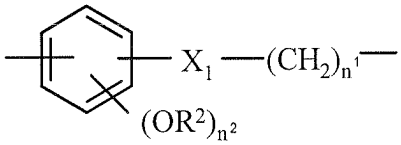


c)



wherein n is an integer from 0 to 20, and $n^1$ is an integer from 1 to 20;

d)

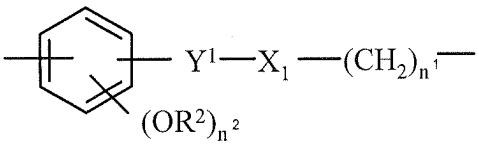


wherein:

$n^1$ is as defined above and $n^2$ is an integer from 0 to 2;

$X_1$ = -OCO- or –COO- and $R^2$ is H or $CH_3$;

e)

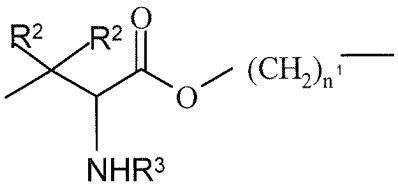


wherein:

$n^1$, $n^2$,$R^2$ and $X_1$ are as defined above;

$Y^1$ is $–CH_2-CH_2-$ or $–CH=CH-(CH_2)_n{}^2-$;

f)

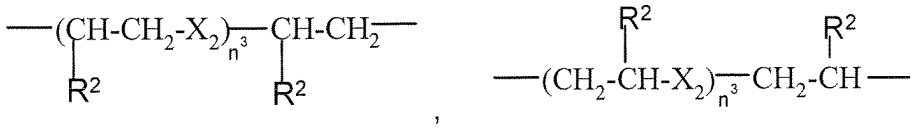


wherein:

$n^1$ and $R^2$ are as defined above, $R^3$ is H or -$COCH_3$;

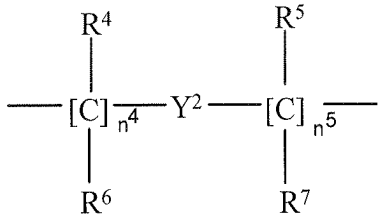
with the proviso that when Y is selected from the bivalent radicals mentioned under b)-f), the $-ONO_2$ group is linked to a $-(CH_2)_{n^1}$ group;

g)



wherein $X_2$ is –O- or –S-, $n^3$ is an integer from 1 to 6, $R^2$ is as defined above;

h)



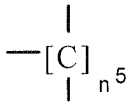
wherein:

$n^4$ is an integer from 0 to 10;

$n^5$ is an integer from 1 to 10;

$R^4$, $R^5$, $R^6$, $R^7$ are the same or different, and are H or straight or branched $C_1$-$C_4$ alkyl;

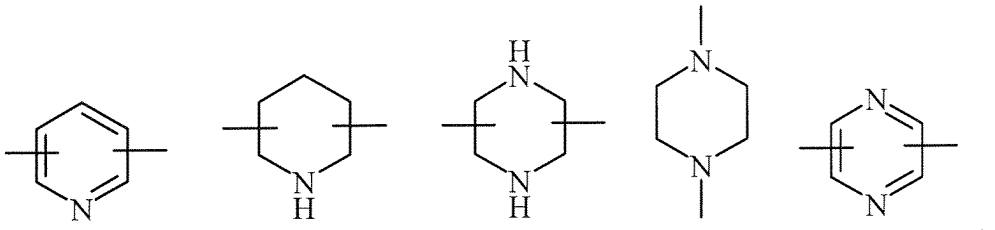
wherein the $-ONO_2$ group is linked to



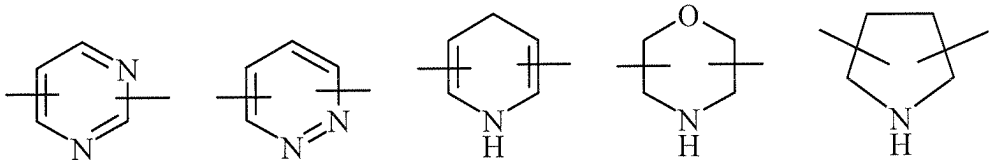
wherein $n^5$ is as defined above;

$Y^2$ is an heterocyclic saturated, unsaturated or aromatic 5 or 6 members ring, containing one or more heteroatoms selected from nitrogen, oxygen, sulfur,

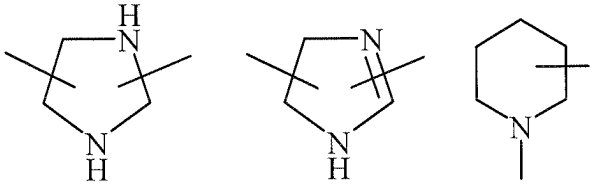
and is selected from



(Y1) (Y2) (Y3) (Y4) (Y5)



(Y6) (Y7) (Y8) (Y9) (Y10)

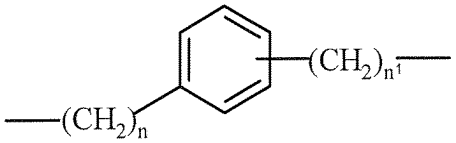


(Y11) (Y12) (Y13)

Claim 2. (Original) A compound of general formula (I) or a pharmaceutically acceptable salt or stereoisomer thereof according to claim 1 wherein Y is a bivalent radical having the following meaning:

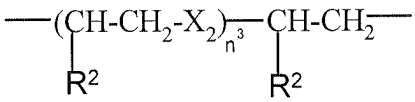
a) straight or branched $C_1$-$C_{10}$ alkylene, being optionally substituted with $T_0$, wherein $T_0$ is as above defined;

b)



wherein n is an integer equal to 0 or 1, and $n^1$ is an integer equal to 1; with the proviso the $-ONO_2$ group is linked to a $-(CH_2)_n{}^1$ group;

g)



wherein $X_2$ is –O- or –S-, $n^3$ is an integer equal to 1 and $R^2$ is H.

Claim 5. (Previously Presented) A method of conferring anti-inflammatory, antithrombotic and antiplatelet activity in a subject, comprising administering to the subject a compound according to claim 1.

Claim 6. (Previously Presented) A method of treatment or prophylaxis of cardiovascular, renal and chronic liver diseases, inflammatory processes and metabolic syndromes in a subject, comprising administering to the subject a compound according to claim 1.

Claim 7. (Previously Presented) A method of treatment or prophylaxis of heart failure, myocardial infarction, ischemic stroke, atherosclerosis, ocular and pulmonary hypertension, hypertension, diabetic nephropathy, peripheral vascular diseases, left ventricular dysfunction and hypertrophy, liver fibrosis and portal hypertension in a subject, comprising administering to the subject a compound according to claim 1.

Claim 8. (Previously Presented) A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a pharmaceutically effective amount of a compound of general formula (I) or a salt or stereoisomer thereof according to claim 1.

Claim 9. (Original) A pharmaceutical composition according to claim 8 in a suitable form for the oral, parenteral, rectal, topic and transdermic administration, by inhalation spray or aerosol or iontophoresis devices.

Claim 10. (Previously Presented) A liquid or solid pharmaceutical composition for oral, parenteral, rectal, topic and transdermic administration or inhalation in the form of tablets, capsules and pills eventually with enteric coating, powders, granules, gels, emulsions, solutions, suspensions, syrups, elixir, injectable forms, suppositories, in transdermal patches or liposomes, containing a compound of formula (I) or a salt or stereoisomer thereof according to claim 1 and a pharmaceutically acceptable carrier.

Claim 11. (Previously Presented)A pharmaceutical composition comprising a compound of general formula (I) of claim 1, at least a compound used to treat cardiovascular disease and a pharmaceutically acceptable carrier.

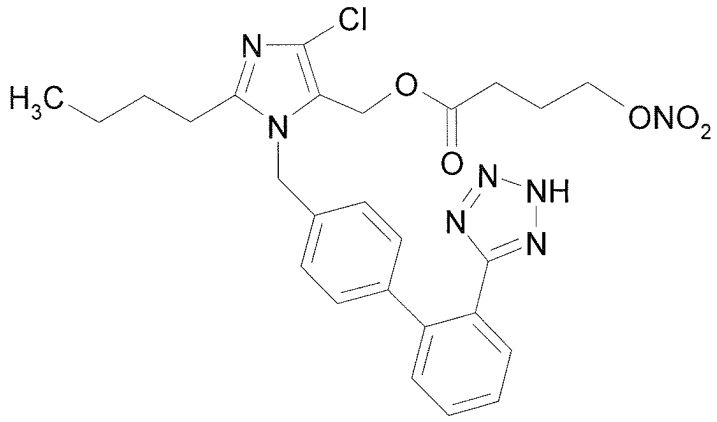
Claim 12. (Previously Presented) A pharmaceutical composition according to claim 11 wherein the compound used to treat cardiovascular disease is selected from the group consisting of: ACE inhibitors, HMGCoA reductase inhibitors, beta-adrenergic blockers, calcium channel blockers, diuretics, antithrombotics such as aspirin, nitrosated ACE inhibitors, nitrosated HMGCoA reductase inhibitors, nitrosated beta-adrenergic blockers, nitrosated aspirin and nitrosated diuretics.

Claim 13. (Original) A pharmaceutical kit comprising a compound of general formula (I) as defined in claim 1, a compound used to treat cardiovascular disease as combined preparation for simultaneous, separated, sequential use for the treatment of cardiovascular disease.

Claim 14. (Original) A pharmaceutical kit according to claim 13 wherein the compound used to treat cardiovascular disease is selected from the group consisting of: ACE inhibitors, HMGCoA reductase inhibitors, beta-adrenergic blockers, calcium channel blockers, diuretics, antithrombotics such as aspirin, nitrosated ACE inhibitors, nitrosated

HMGCoA reductase inhibitors, nitrosated beta-adrenergic blockers, nitrosated aspirin and nitrosated diuretics.

Claim 15. (Previously Presented) A compound having the following formula (2):




(2)

or a pharmaceutically acceptable salt or stereoisomer thereof.

Claim 18. (Previously Presented) A compound according to claim 1, wherein Y is a straight or branched $C_1$-$C_{10}$ alkylene.